

Falk lecture provides evolutionary insights into endocrine disruption

By Robin Arnette

Evolutionary biologist Joseph Thornton, Ph.D., was invited to NIEHS April 14 to present the 2014 Hans L. Falk Memorial Lecture. His talk, "The Evolutionary History of Steroid Hormone Receptors: Ancient Insights Into Endocrine Disruption," focused on what he's learned about the evolution of steroid hormone receptors and the implications for endocrine disruption. The seminar was hosted by David Armstrong, Ph.D., head of the NIEHS Membrane Signaling Group.

Thornton

(<http://genes.uchicago.edu/contents/faculty/thornton-joe.html>)

said he chose to study steroid hormone receptors because they are often the targets of environmental toxicants, and they are excellent models for studying the evolution of protein complexity.

What's the connection between evolution and endocrine disruption? "If we want to understand why a biological process exists, or what makes it normal or abnormal, we need to understand its history," Thornton said, "as, in society, understanding the current state of our culture or politics is greatly enriched if we understand how it got this way."

Bringing the past back to life

As members of a larger nuclear receptor superfamily, steroid hormone receptors play crucial roles in the regulation of metabolism and have key functions in the development of cancer and endocrine disruption. Each receptor binds a particular hormone, such as estrogen or cortisol, with extraordinary affinity and specificity.

To study the evolutionary processes that led to this specificity, Thornton's team developed a strategy called ancestral gene resurrection, which involved cloning the genes from many primitive organisms, testing which hormones could activate them efficiently, and determining their three-dimensional structures at the atomic level.

Using this information, the researchers examined a large database containing gene sequences of present-day steroid receptors and developed a phylogenetic tree, a diagram that shows evolutionary relationships among species. Next, Thornton's team employed a statistical method, which relied on models of the evolutionary process, to examine the probability of an amino acid mutating to another amino acid across the tree. Once they generated plausible genetic sequences, they synthesized DNA to code for those ancestral proteins, expressed them in cultured cells, and characterized their functions biochemically.

Genetic divergence

The results suggested that the first steroid receptor was an estrogen receptor that evolved approximately 450 million years ago. This estrogen-specific steroid receptor 1 (SR1) gave rise to an SR2, which bound to progesterone rather than estrogen. Thornton's data suggested that the new function occurred as a result of metabolic changes that produced new hormones, as well as genetic variation in the receptor that made it selective for a new hormone.

"Once we were able to identify the mutations that caused the evolutionary changes in function," Thornton explained, "we used structural biology to understand the physical mechanisms that mediated ancient genetic change and the effect on estrogen receptors."

Thornton summed up the implications for endocrine disruption by pointing out that receptors evolved to be only as specific as necessary. Before the evolution of additional hormones and the gene duplications that gave rise to the extended steroid receptor family, there was little pressure on the original receptor to be very precise. This helps explain why so many environmental toxicants, or xenoestrogens, can activate estrogen receptors and thereby disrupt normal physiological processes.



Thornton is a professor in the Department of Human Genetics, and Department of Ecology and Evolution at the University of Chicago. He is also a professor at the Center of Ecology and Evolutionary Biology at the University of Oregon. (Photo courtesy of Steve McCaw)



Armstrong, head of the NIEHS Membrane Signaling Group, hosted the seminar. (Photo courtesy of Steve McCaw)



NIEHS Calcium Regulation Group head James Putney, Ph.D., foreground, and Scientific Director Darryl Zeldin, M.D., to his left, were part of the full house attending the lecture. (Photo courtesy of Steve McCaw)



NIEHS Deputy Director Richard Woychik, Ph.D., presented Thornton with the Hans L. Falk Memorial plaque, as members of the Falk family looked on. Shown, from left, are Woychik, Thornton, Raymond Falk, Ph.D., Gabrielle Falk, and Donald Falk, M.D. Falk's widow has attended every one of the Falk lectures. (Photo courtesy of Steve McCaw)

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